CORRESPONDENCE

Re: Are Women More Susceptible to Lung Cancer?

In a recent editorial in the Journal (1), Blot and McLaughlin criticize our case–control study (2) and other case–control studies in comparison with cohort studies addressing smoking-related lung cancer risks in males and females. In the same issue of the Journal, Bain et al. (3) also criticize our study. Both sets of authors point out that a number of carefully conducted cohort studies have shown no measurable excess of lung cancer rates in female smokers compared with male smokers, once amounts of smoking have been controlled, whereas our study showed statistically significantly and substantially higher risks for females than for males at every level of smoking. The authors offer various explanations for this discrepancy, including our use of relative risk measures, potential recall biases, interviews with next of kin, and so on (1). However, the answer lies elsewhere. Bain et al. (3) and the other cohort studies [reviewed in (3)] examined risks for males and females, adjusted for amount of smoking. In these studies, the scientific question addressed was, Adjusted for dose of smoking (in the same way for males and females), are males and females, or are male and female smokers, at the same risk? In other words, What is the (main) effect of sex, given adjustment for smoking? By contrast, the scientific question addressed by our case–control study and others was, At a given dose of smoking, is the effect of smoking different for males and females? That is, do males and females have different relationships between their smoking doses and risk of lung cancer (i.e., a different risk sensitivity to the effects of smoking)? This question is not addressed by the analyses of Bain et al. (3) and the others, which do not involve effect modification of smoking by gender. In a statistical model, if men and women are forced to have the same relationship between smoking and risk of lung cancer, then what is being examined is the intrinsic risk of sex itself, not of smoking. Because the major identified cause of lung cancer is tobacco smoking, we think the effect of sex by itself is of secondary importance.

Should Bain et al. (3) examine different smoking dose–risk sensitivities between males and females in their data, they will face another issue. Ten cohort studies of lung cancer to date [cited by Bain et al. (3) and by us (4)] show that the baseline risk of lung cancer among female nonsmokers is approximately 75% of the baseline risk among male nonsmokers (Table 1). These 10 studies collectively identified thousands of lung cancer cases among nonsmokers in their cohorts. Bain et al. (3) found 99 female and 33 male lung cancer cases among their nonsmokers, with annual incidence rates per 100 000 of 16 and 12, respectively, or a female: male ratio of 1.33. This finding is at variance (approximately \( P = .005 \)) with the large amount of evidence from the other 10 cohort studies and suggests that some systematic biases underlie either the reporting of smoking or the incidence of lung cancer in their cohort. A nonsmoker baseline absolute risk higher for females than males will, by artifact, reduce any relative risks for females compared with males in the smoking-related risk sensitivities to lung cancer calculated with the data of Bain et al. (3).

Thus, it is by no means clear that female smokers have the same smoking dose-related risks of lung cancer as males. Until sufficient analyses addressing this specific question show such a finding, the evidence to date indicates that female smokers are more sensitive than male smokers to the effects of smoking in inducing lung cancer.

**Harvey A. Risch**

**Anthony B. Miller**

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**Table 1. Rates of lung cancer among nonsmoking males and females in 10 cohort studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Female rate†</th>
<th>Male rate†</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swedish study</td>
<td>Incidence</td>
<td>15</td>
<td>19.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Denmark study</td>
<td>Incidence</td>
<td>similar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaiser-Permanente study</td>
<td>Mortality</td>
<td>8</td>
<td>24</td>
<td>0.33</td>
</tr>
<tr>
<td>British Physicians Study</td>
<td>Mortality</td>
<td>7</td>
<td>10</td>
<td>0.70</td>
</tr>
<tr>
<td>10% U.S. National Mortality study</td>
<td>Mortality</td>
<td>9.4</td>
<td>12.5</td>
<td>0.75</td>
</tr>
<tr>
<td>American Cancer Society CPS-I study</td>
<td>Mortality</td>
<td>13.3</td>
<td>15.6</td>
<td>0.85</td>
</tr>
<tr>
<td>American Cancer Society CPS-II study</td>
<td>Mortality</td>
<td>12.6</td>
<td>15.2</td>
<td>0.83</td>
</tr>
<tr>
<td>Japanese Six-Prefecture Study</td>
<td>Mortality</td>
<td>18.4</td>
<td>24.1</td>
<td>0.76</td>
</tr>
<tr>
<td>Canadian study</td>
<td>Mortality</td>
<td>12.8</td>
<td>16.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Scotland study</td>
<td>Mortality</td>
<td>24</td>
<td>32</td>
<td>0.75</td>
</tr>
</tbody>
</table>

†Rate previously cited (3,4).

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**REFERENCES**


**NOTES**

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**RESPONSE**

Drs. Risch and Miller state that we (1) and Bain et al. (2) criticize their earlier case–control study of lung cancer, and they purport to offer an alternative explanation for the discrepancy between the findings of case–control and cohort studies examining differences in lung cancer risk between men and women. They state (we believe incorrectly) that whereas the case–control studies have addressed the statistical interaction between smoking and sex on the risk of lung cancer, the cohort studies have examined only the main effects of sex. They conclude that current evi-

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dence indicates that female smokers are more susceptible to smoking-induced lung cancer than male smokers.

We would not characterize our comments on the Risch et al. (3) case–control study as criticism; indeed, we simply described the study’s findings of higher odds ratios among women than men across smoking categories. We did note that the focus of case–control studies is the estimation of relative risks of lung cancer among smokers compared with never smokers, whereas the cohort studies, including that of Bain et al. (2), compare actual incidence or mortality rates of lung cancer among men and women at similar levels of smoking. When the cohort studies examine rates of lung cancer among men and women with equivalent amounts smoked, they show consistently that the rates are about the same or even somewhat less for women. Thus, the studies clearly indicate that the probability of developing lung cancer is about the same in men and women when approximately equal smoking histories are considered.

Estimates of relative risk from case–control studies such as that of Risch et al. (3) are sensitive to variation in lung cancer risk among never smokers and, thus, the demonstration of effect modification by sex cannot automatically be interpreted as providing evidence for a difference in susceptibility by sex. The estimates of male–female differences in lung cancer incidence from cohort studies such as Bain et al. (2) are based only on smokers themselves and, to the extent that men and women have comparable exposure to tobacco carcinogens in the strata defined by smoking histories, these estimates provide a direct evaluation of gender differences in susceptibility. Risch and Miller argue that among never smokers, women tend to have lower rates of lung cancer than men. However, male and female nonsmokers may differ in numerous other ways that may influence their risk of lung cancer. Accounting for such occupational, environmental, lifestyle, medical, or other risk factors among nonsmokers is difficult, because smoking is such a dominant cause of lung cancer that there typically are only small numbers of case patients who have never smoked (4). Furthermore, in the cohort studies, if relative risks of lung cancer among smokers versus never smokers were to be calculated, they would not always be higher among females than males. Indeed, in the large CPS-II study cited in the tables presented by Bain et al. (2) and Risch and Miller, the male-to-female ratio in lung cancer rates was greater among smokers (adjusted for amounts smoked) than among nonsmokers.

Although it is not implausible that men and women may respond to tobacco carcinogens differently, the existing cohort studies, including that from Bain et al. (2), suggest that such differences have not had a marked effect on lung cancer rates. Thus, the conclusion of Risch and Miller that the "evidence to date indicates that female smokers are more sensitive than male smokers to the effects of smoking in inducing lung cancer" seems premature and not supported by the available cumulative epidemiologic data.

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RESPONSE

Risch and Miller raise a number of points regarding our study design and the central message of our paper (1)—that similar doses of cigarette smoke led to similar rates of lung cancer in men and women. Our view was based on evidence from a consistent set of findings from all published prospective data (from seven cohort studies) bearing on this issue and supported by our new primary data analysis comparing lung cancer incidence rates of female smokers from the Nurses’ Health Study with those of male smokers from the Health Professionals Follow-up Study. Nothing in Risch and Miller’s letter gives any cause for doubting these data. The central tenet of our reasoning, not addressed in their letter, is that the only direct way to address the true underlying force of morbidity from smoking is by measuring dose-specific incidence rates (which they do not mention were displayed in some detail). Comparing these incidence rates among men and women allows us to look at exactly what we want to know. It also prevents the comparison from being distorted by the unstable, and thus variable, lung cancer rates among nonsmokers in different populations, an unavoidable problem when contrasting two relative measures (although Risch and Miller still seem to favor this approach). This potential distortion is precisely why nonsmokers were excluded from all analyses we reported, contrary to what Risch and Miller seem to imply in their second paragraph. We hope readers clearly understand that the implication of the findings from all cohort studies and from general population trends (2) is that the public health issues for men and women are the same.

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REFERENCES


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